Remarks/Arguments:

Claims 2 and 4-6 are amended to correct a typographical error and promote clarity of the claims. New claims 58-60 are added. Support for new claims 58-60 can be found, e.g., at page 17, lines 7-19 of the specification. Note that nt 244-265 of the integrin β1 gene (GenBank Accession No. NM 002211.2) is located within an exon of the integrin β1 gene (see Exhibit A). No new matter is introduced.

Claims 1-8, 11, 19, and 58-60 are pending in the application. Reexamination and reconsideration of the application, as amended, are respectfully requested.

CLAIM REJECTIONS UNDER 35 USC § 102(e)

Claims 1, 3, 7, 11, and 19 are rejected as being anticipated by US 2003/0084471 to Beach et al. ("Beach"). Applicants respectfully traverse.

Claims 1 and 7 are directed to an isolated RNA comprising an artificial intron RNA that is released in a cell such as a eukaryotic cell, thereby silencing the function of a target gene. On the other hand, Beach discloses methods and compositions for RNA interference through double-stranded RNA (dsRNA). Although Beach mentions that an intronic sequence can be cloned into an expression vector for producing dsRNA, it suggests nothing whatsoever about creating an antificial intron RNA that can be released in a cell, thereby silencing the function of a target gene. To the contrary, Beach teaches only naturally-occurring introns. For example, Beaches states at page 2, right column, paragraph [0020]:

> [0020] Another aspect of the present invention provides a method for attenuating expression of a target gene in cultured cells, comprising introducing an expression vector having a "non-coding sequence" which, when transcribed, produces double stranded RNA (dsRNA) in the cell in an amount sufficient to attenuate expression of the target gene. The non-coding sequence may include intronic or promoter sequence of the target gene of interest, and the dsRNA comprises a

> nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence of the promoter or intron of the target gene ...(Emphasis added)
>
> Beaches also states at page 9, right column, paragraph [0115]:
>
> [0115] As used herein, the term "gene" or "recombinant gene" refers to a nucleic acid comprising an open reading frame encoding a polypeptide of the present invention, including both exon and (optionally) intron sequences. The nucleic acid may also optionally include non-coding sequences such as promoter or enhancer sequences. A "recombinant gene" refers to nucleic acid encoding such regulatory polypeptides, that may optionally include intron sequences that are derived from chromosomal DNA. The term "intron" refers to a DNA sequence present in a given gene that is not translated into protein and is generally found between exons. (Emphasis added)

Since Beach fails to teach an artificial RNA required by claims 1 and 7, it cannot anticipate claim 1 or 7. Claims 3, 11, and 19, dependent from claim 1, are also novel over Beach for at least the same reasons. Withdrawal of the rejections is thus respectfully requested.

CLAIM REJECTIONS UNDER 35 USC § 103(a)

Claims 1-8, 11, and 19 are rejected as being unpatentable over Beach in view of US 6,013,487 to Mitchell ("Mitchell"), Krawczak et al. (1992) Hum Genet 90:41-54 ("Krawczak"), Zhuang et al. (1989) PNAS 86:2752-2756 ("Zhuang"), and Coolidge et al. (1997) Nucleic Acids Research 25:888-896 ("Coolidge"). Applicants respectfully traverse.

Claims 1 and 7-8 are directed to an isolated RNA comprising an artificial intron RNA that is released in a cell such as a eukaryotic cell, thereby silencing the function of a target gene. As discussed above, Beach fails to teach such an RNA. Likewise, none of the secondary references cited by the Examiner discloses such an

RNA, and the Examiner did not rely on these references for disclosing such an RNA. Instead, the Examiner relied on the cited references for teaching a splice acceptor site (Mitchell), splice donor site (Krawczak), branch site (Zhuang), and poly-pyrimidine tract (Coolidge), respectively. As such, none of the secondary references can cure the defects of Beach.

Further, contrary to the Examiner's statement, one skilled in the art would not have been motivated to combine Beach and the secondary references to come up with the claimed invention. As discussed above, Beach discloses methods and compositions for RNA interference through dsRNA. Formation of such dsRNA does not depend on RNA splicing at all. See, e.g., EXAMPLE 3 at page 20, right column, paragraph [0219] – page 21, left column, paragraph [0223]; EXAMPLE 5 at page 22, right column, paragraphs [0242] – [0245]; EXAMPLE 7 at page 23, paragraphs [0251] – [0253] in Beach. Therefore, one skilled in the art would not have been motivated to modify the naturally-occurring intron sequences taught by Beach by replacing the splice acceptor sites, splice donor sites, branch sites, and poly-pyrimidine tracts in these introns with those taught by Mitchell, Krawczak, Zhuang, and Coolidge.

In light of the forgoing, Applicants respectfully submit that the prior art references cited by the Examiner, alone or in combination, do not render claims 1 and 7-8 obvious. Claims 2-6, 11, and 19, dependent directly or indirectly from claim 1, are also patentable over the cited art for at least the same reasons. Therefore, the rejections should be withdrawn.

CONCLUSION

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles, California telephone number (310) 785-4600 to discuss the steps necessary for placing the application in condition for allowance.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-1314.

Respectfully submitted,
HOGAN & HARTSON L.L.P.

Date: May 26, 2009

By: /yjluo/
Y. Jenny Luo, Ph.D.
Registration No. 54,284
Attorney for Applicants

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Los Angeles, California 90067
Phone: 310-785-4600
Fax: 310-785-4601

Exhibit A

NCBI Reference Sequence: NM_002211.2

gi|19743812|ref|NM_002211.2|

This record has been replaced by NM_002211.3

Comment Features Sequence

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linear   PRI 16-MAR-2008
DEFINITION  Homo sapiens integrin, beta 1 (fibronectin
receptor, beta
            polypeptide, antigen CD29 includes MDF2, MSK12)
(ITGB1), transcript
            variant 1A, mRNA.
ACCESSION   NM_002211
VERSION     NM_002211.2  GI:19743812
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
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Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Primates;
Haplorrhini;
            Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 3700)
  AUTHORS   Bhoopathi,P., Chetty,C., Kunigal,S.,
Vanamala,S.K., Rao,J.S. and
            Lakka,S.S.
  TITLE     Blockade of tumor growth due to matrix
metalloproteinase-9
            inhibition is mediated by sequential activation
of beta1-integrin,
            ERK, and NF-kappaB
  JOURNAL   J. Biol. Chem. 283 (3), 1545-1552 (2008)
   PUBMED   17991734
  REMARK    GeneRIF: These results indicate that MMP-9
inhibition induces
            apoptosis due to altered beta1-integrin
expression in
            medulloblastoma and ERK activation plays an
active role and
            functions upstream of NF-kappaB activation to
initiate the
            apoptotic signal.
REFERENCE   2  (bases 1 to 3700)
  AUTHORS   Saidi,S., Mahjoub,T., Slamia,L.B., Ammou,S.B.,
Al-Subaie,A.M. and
```

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            Almawi,W.Y.
  TITLE     Association of human platelet alloantigen 1
through 5 polymorphisms
            with ischemic stroke
  JOURNAL   Cerebrovasc. Dis. 25 (1-2), 81-86 (2008)
   PUBMED   18057877
  REMARK    GeneRIF: Observational study of gene-disease
association. (HuGENet)
REFERENCE   3  (bases 1 to 3700)
  AUTHORS   Bolduc,G.R. and Madoff,L.C.
  TITLE     The group B streptococcal alpha C protein binds
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that promotes
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cells
  JOURNAL   Microbiology (Reading, Engl.) 153 (PT 12), 4039-
4049 (2007)
   PUBMED   18048918
  REMARK    GeneRIF: Group B streptococci ACP binds alpha(1)
beta(1)-integrin
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internalization within
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REFERENCE   4  (bases 1 to 3700)
  AUTHORS   Hu,K., Wu,C., Mars,W.M. and Liu,Y.
  TITLE     Tissue-type plasminogen activator promotes
murine myofibroblast
            activation through LDL receptor-related protein
1-mediated integrin
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  JOURNAL   J. Clin. Invest. 117 (12), 3821-3832 (2007)
   PUBMED   18037995
  REMARK    GeneRIF: tPA induces LRP-1 tyrosine
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myofibroblast
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REFERENCE   5  (bases 1 to 3700)
  AUTHORS   Yao,K., Tan,J., Ye,P., Wang,K., Xu,W., ShenTu,X.
and Tang,X.
  TITLE     Integrin beta1-mediated signaling is involved in
transforming
            growth factor-beta2-promoted migration in human
lens epithelial
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  JOURNAL   Mol. Vis. 13, 1769-1776 (2007)
   PUBMED   17960115
  REMARK    GeneRIF: TGF-beta2 promoted human lens
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mediated signaling
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and migration in
            human lens epithelial cells.
            Publication Status: Online-Only
REFERENCE   6  (bases 1 to 3700)
  AUTHORS   Languino,L.R. and Ruoslahti,E.
  TITLE     An alternative form of the integrin beta 1
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JOURNAL J. Biol. Chem. 267 (10), 7116-7120 (1992)
PUBMED 1551917
REFERENCE 7 (bases 1 to 3700)
AUTHORS Otey,C.A., Pavalko,F.M. and Burridge,K.
TITLE An interaction between alpha-actinin and the beta 1 integrin subunit in vitro
JOURNAL J. Cell Biol. 111 (2), 721-729 (1990)
PUBMED 2116421
REFERENCE 8 (bases 1 to 3700)
AUTHORS Sonnenberg,A., Linders,C.J., Modderman,P.W., Damsky,C.H., Aumailley,M. and Timpl,R.
TITLE Integrin recognition of different cell-binding fragments of laminin (P1, E3, E8) and evidence that alpha 6 beta 1 but not alpha 6 beta 4 functions as a major receptor for fragment E8
JOURNAL J. Cell Biol. 110 (6), 2145-2155 (1990)
PUBMED 1693624
REFERENCE 9 (bases 1 to 3700)
AUTHORS Vogel,B.E., Tarone,G., Giancotti,F.G., Gailit,J. and Ruoslahti,E.
TITLE A novel fibronectin receptor with an unexpected subunit composition (alpha v beta 1)
JOURNAL J. Biol. Chem. 265 (11), 5934-5937 (1990)
PUBMED 2138612
REFERENCE 10 (bases 1 to 3700)
AUTHORS Bodary,S.C. and McLean,J.W.
TITLE The integrin beta 1 subunit associates with the vitronectin receptor alpha v subunit to form a novel vitronectin receptor in a human embryonic kidney cell line
JOURNAL J. Biol. Chem. 265 (11), 5938-5941 (1990)
PUBMED 1690718

COMMENT REVIEWED REFSEQ: This record has been curated by NCBI staff. The reference sequence was derived from X07979.1, BC020057.1 and X68969.1.
[WARNING] On Apr 11, 2008 this sequence was replaced by gi:162519230.
On Mar 26, 2002 this sequence version replaced gi:4504766.

Summary: Integrins are heterodimeric proteins made up of alpha and beta subunits. At least 18 alpha and 8 beta subunits have been described in mammals. Integrin family members are membrane receptors involved in cell adhesion and recognition in a variety of processes including embryogenesis, hemostasis, tissue repair, immune response and metatastatic diffusion of tumor cells. The protein encoded by this gene is a beta subunit. Six alternatively spliced variants have been found for this gene which encode five proteins with alternate carboxy termini.

Transcript Variant: This variant (1A) is the most common variant and has an alternate 5'UTR due to the use of the alternate proximal promoter. Variants 1A and 1E encode the same isoform.

Publication Note: This RefSeq record includes a subset of the publications that are available for this gene. Please see the Entrez Gene record to access additional publications.
COMPLETENESS: full length.

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